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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/390,634	09/07/1999	PAUL J. PRICE	0942.4190002	7270

26111 7590 09/27/2006

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EXAMINER	
WOITACH, JOSEPH T	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 09/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/390,634	PRICE ET AL.	
	Examiner	Art Unit	
	Joseph T. Woitach	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 May 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *176-201,204-223,226-241,243-265 and 268-282* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *176-201,204-223,226-241,243-265 and 268-282* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This application is a divisional of application 08/781,772, filed January 10, 1997, now abandoned.

Examiner's Comment

To make clear the record, as indicated by Applicants Examiner acknowledges that the office action mailed November 2, 2005, was a non-final office action.

Applicants amendment filed May 2, 2006, has been received and entered. Claims 1-175, 202, 203, 224, 225, 242, 266, 267 have been cancelled. Claims 176, 178, 179-182, 188, 190-194, 210, 212-214, 232, 241, 249-251, 253-255, 263, 274-282 have been amended. Claims 176-201, 204-223, 226-241, 243-265, 268-282 are pending and currently under examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 176-201, 204-223, 226-241, 243-265, 268-282 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition of mouse embryonic stem cells and serum-free media capable of preventing differentiations of mouse embryonic stem cells, and the methods of use of said composition, does not reasonably

provide enablement for other combinations of media and embryonic stem cells from any other animal.

Applicants note the amendment to the claims to encompass mouse or primate embryonic stem cells, and point to the information provided in the declaration of Paul Price and Mary Tilkins filed November 12, 2002 for successfully culturing mouse, human and embryonic stem cells. Applicants argue that given the requirements of 35 USC 112, first paragraph, the present specification enables the invention as claimed. See Applicants' amendment, pages 27-29. Applicants' arguments have been fully considered, but not found persuasive.

Examiner acknowledges that the compositions and methods encompassing mouse embryonic stem cells are enabled. More specifically, given the breadth of the claims one can provide a serum free media containing LIF which would provide the functional limitation of the claims for preventing differentiation of the mouse ES cells. The factors added to media necessary to culture mouse ES cells where known at the time of filing, however LIF will not provide this function for primate ES cells. Further, neither at the time of filing nor in the present specification is there a teaching for a factor such as LIF to be added to the media which will prevent the differentiation of primate ES cells. This is specifically supported by Applicants' specification teaching of conditions which allow ES cells to differentiate (page 42, Example 6). At issue is the breadth and requirements of the claims. By example, independent claim 176 recites "a serum-free culture medium capable of preventing differentiation", which is being interpreted to require that the media provide this function, not some other factor. At the time of filing the only condition known in the art which prevents primate ES cells from differentiating is the culturing of the cells on a fibroblast feeder layer. The information provided in the

declaration and cited supporting references has been fully considered, but clearly appears to support the position that human cells must be cultured on a fibroblast feeder layer. Examiner would acknowledge that a serum supplement can substitute for serum, as is evidenced by the use of KnockOut SR instead of serum in the cited references, however this fails to support the ability of such a supplement by itself to prevent differentiation. It is noted that even for mouse cells, it would be maintained that it is not a serum supplement that is preventing the differentiation of the mouse ES cells, rather it is the presence of LIF in the media (see again support in the specification at page 42). At the time of filing it was well known that an effective amount of LIF in the culture media would prevent the differentiation of mouse ES cells. LIF does not have this ability or function for primate ES cells. With respect to other general methods, as set forth in previous office actions, the art makes evident that the conditions used to obtain and maintain mouse ES cell fails to work for other species, most notably to date is the difference in the affect of LIF on mouse and primate ES cells in culture (see previous office actions).

Again, the courts have stated that reasonable correlation must exist between scope of exclusive right to patent application and scope of enablement set forth in patent application. 27 USPQ2d 1662 *Ex parte Maizel.* The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations."

(*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

Thus it is maintained, that in view of the quantity of experimentation necessary to determine the parameters listed above, the lack of direction or guidance provided by the specification, the absence of working examples for the demonstration or correlation to the production of embryonic stem cells from other animals and the appropriate media for preventing differentiation, and the general unpredictable state of the art with respect to the isolation and properties of the resulting embryonic stem cell with its unique properties and requirements needed to maintain it in an undifferentiated state, it would have required undue experimentation for one skilled in the art to make and/or use the claimed inventions as broadly claimed.

Claim Rejections - 35 USC 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 176-201, 204-223, 226-241, 243-265, 268-282 stand rejected under 35 U.S.C. 103(a) as obvious over Ponting (US Patent 5,405,772), Gibco BRL Products and Reference Guide ((1997) Chapters 5 and 8) and Atsumi *et al.* (Develop. Growth & Differ. 35(1):81-87 (1993)).

Applicants provide a summary of the requirements for making a proper rejection under 35 USC 103, and note that the claims recite a functional requirement "of preventing differentiation of the embryonic stem cells during expansion of the embryonic stem cells" and argue that none of the references provide conditions that prevent cell differentiation (bridging pages 29-30). Applicants argue that there is no motivation to combine, nor expectation of success, and that the rejection is based on an improper obvious to try standard (citing *In re O'Farrell*). See Applicants amendment, pages 29-32. Applicants arguments have been fully considered, but not found persuasive.

Applicants' arguments are not found persuasive because the functional limitation relied upon is not provided by the synthetic serum taught in the instant disclosure, rather it is obtained by culturing mouse or human ES cells on feeder cells or in the case of the mouse ES cells by providing LIF to the culture. Applicants arguments that the cited art fails to anticipate the

claimed invention is unpersuasive because the guidance provided in the references anticipates the breadth of the claims. There is nothing in KnockOutSR that would cause differentiation, nor is there anything in any of the other cited references. To the contrary, each provide conditions to maintain ES cells in an undifferentiated state. Applicants have previously argued that Ponting failed to provide the necessary guidance to obtain a media which would not differentiate ES cells is not found convincing because it is the serum that causes differentiation, not the basal media, and by providing a completely synthetic media the cited art provides the necessary guidance to obtain a media which would not differentiate ES cells. Moreover, it is noted that other factors besides the generality of the media, such as the presence of LIF for mice is feeder free conditions, that provides the condition wherein ES cells do not differentiate.

The specification teaches and recognizes that prior art acknowledges the problems of various sources of serum (see for example pages 2-3 of the specification), and it was routine in culturing ES cells to test various lots of serum for its ability to maintain the ES cell line (page 3). The motivation to use a synthetic media/serum is to provide a reproducible source of material so that testing, purchasing and storing batches of serum would not be required. As previously noted, many claims do not include any specific structural components, only a functional limitation of the media. The combination of cited references provides the necessary guidance and details for providing a synthetic serum supplement. The present specification fails to teach what components in serum cause differentiation or toxicity to ES cells in culture, and only provide a broad outline of serum supplement components that is also taught by the cited references. Moreover, it is noted that the claims are so broad as not to recite nor require a serum supplement at all, only a functional limitation. The combination of teachings of the cited references provides

all the necessary guidance and detail to anticipate the limitations of the claims with a great expectation of success.

As noted in the previously, the art teaches that provides evidence that at the time of filing and issuance of Ponting serum-free conditions for culturing embryonic stem cells were known and used (see guidance of Atsumi *et al.*). Atsumi *et al.* teach to use as a serum supplement serum-free media that are obtained as a conditioned media. Using such media Atsumi *et al.* were able to define specific factors supplied by the feeder cells in order to make a complete serum-free media. Ponting clearly provides motivation and anticipation of the specific embodiments required to make a synthetic serum supplement. While Ponting does not specifically disclose all the specific components listed in the claims, the use of these components would be obvious because they are factors commonly used in cell culture. Further, Ponting teaches that the media should be as defined as possible and optimized for a given cell type, therefore one would be motivated to use and test the various forms of these components for their specific affects on the cells in culture. For example lipid-rich/poor albumin provides a more defined source of albumin, lacking lipids that could affect the cells. Moreover, Ponting teaches that the components can be synthetic (column 11, lines 65-68), wherein a synthetic component would represent a more defined molecule free from potential contaminants that may be present in naturally isolated sources.

Importantly, upon review of the present specification, there is no specific teaching that any one of the components recited or encompassed by the instant claims provides any unexpected affect on the cultured cells that would not have been readily known in the art, such as the use of LIF or feeder cells to maintain embryonic stem cells in culture. The level of

knowledge and skill in the art for culturing cells is high, and there would be a reasonable motivation and expectation of success to use specific components from various sources as provided by Ponting to provide for a more defined and optimized media.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (571) 272-0739.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached at (571) 272-0735.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (571) 272-0532.

Joseph T. Woitach